B1 cont 2. (amended) The polynucleotide of Claim 1 wherein the polynucleotide sequence comprises the sequence [substantially] as depicted in SEQ ID NO:2.

B2 4. (amended) An [antisense molecule] oligonucleotide comprising [the] a complement of the polynucleotide of Claim 2 [or a biologically-effective portion thereof].

8. (amended) A method for producing cells which express a biologically active polypeptide comprising a sequence having at least 85% total sequence similarity to [substantially as depicted in] SEQ ID NO:3, or a biologically active fragment thereof, said method comprising:

sub C2 a) transforming suitable host cells with a polynucleotide comprising a nucleic acid that encodes a polypeptide comprising a sequence having at least 85% total sequence similarity to SEQ ID NO:3 or a biologically active fragment thereof, and [culturing a host cell according to Claim 5 under conditions suitable for the expression of said polypeptide].

b) selecting cells capable of expressing the biologically active polypeptide encoded by the introduced nucleic acid.

B3 9. (amended)A method for producing a polypeptide [having the amino acid sequence substantially as depicted in] comprising a sequence having at least 85% sequence similarity to SEQ ID NO:3, said method comprising the steps of:

a) culturing a host cell according to Claim 5 under conditions suitable for the expression of said polypeptide, and

b) recovering said polypeptide from the host cell culture.

Remarks concerning the requested amendments:
Applicants herein address all outstanding substantive issues.

RESPONSE

Applicant acknowledges the Examiner's comments at paragraph 4 of the Action and will provide suitably amended figures and descriptions thereof at a later date.

The applicant hereby states that the content of the paper and the computer readable copies of the sequence listing are the same and therefor introduce no new subject matter.

THE REJECTION OF CLAIMS UNDER 35 USC § 112 PARAGRAPH 2

The pending claims were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter the Applicants regard as the invention.

Applicants have addressed these rejections by changing the "substantially as depicted" language from claims 1, 2, 8 and 9 to cover polypeptides with "at least 85% total amino acid similarity".

The specification specifically defines variants at p.23, line 16:

> The present invention also encompasses variants of the human brain-derived potassium channel molecule SEQ ID NO:3. A preferred variant substantially as depicted in SEQ ID NO:3, for instance, is one having at least 85% total amino acid sequence similarity; a more preferred variant is one having at least 90% total amino acid sequence similarity; and a most preferred variant is one having at least 95% total amino acid sequence similarity to the human brain-derived potassium channel amino acid sequence (SEQ ID NO:3) or a biologically active fragment thereof.

With regard to the indefiniteness of the terms "biologically active or "biologically effective", the Applicants disagree that these terms are indefinite. At page 10, first paragraph it is stated:

> Biological activity as used herein refers to the ability to allow transmembrane potassium ion flow and/or transport or regulate transmembrane potassium ion flow and/or transport or the ability of a subunit to bind another subunit, ligand, or cofactor and/or otherwise modulate the pharmacological activity of a potassium channel.

Page 11, line 14 states:

> Methods of identifying compounds that modulate the activity of a potassium channel polypeptide are generally preferred, which comprise combining a candidate compound

modulator of a potassium channel biological activity with a polypeptide of a potassium channel having the sequence substantially as depicted in SEQ ID NO:3, and measuring an effect of the candidate compound modulator on the biological activity of the potassium channel (e.g., physical binding interaction, ability to pass K+ ions, neurophysiological effect on neurons).

The invention is clearly directed to a potassium channel receptor whose main function is to allow transmembrane potassium ion flow. The specification does therefore precisely define what is meant by "biological activity".

Claim 8 has been amended to correctly recite "A method for producing cells". Support for this amendment can be found on page 28, line 25.

THE REJECTION OF CLAIM 4 UNDER 35 USC § 112 PARAGRAPH 1

The Examiner has remarked that the specification is enabled for an oligonucleotide that is complementary to the mRNA encoding a polypeptide of SEQ ID NO:3. Claim 4 has been amended to cover an oligonucleotide complementary to SEQ ID NO: 2 (which is the cDNA coding for the polypeptide of SEQ ID NO:3).

THE REJECTION OF CLAIMS UNDER 35 USC § 102(a)

Claims 1-5 and 8 stand rejected as being anticipated by Yokoyama *et al.*

The Applicants have discovered a novel human brain-derived splice variant potassium channel protein which is 854 amino acid residues in length. The polypeptide of Yokoyama is only 393 amino acid residues long and actually represents a "short splice variant" of the KCNQ2 gene. This short splice variant is expressed in different stages of neuronal development to that of the present invention. The polypeptide of the present invention is prominent in adult brain and in mature neurons, while the Yokoyama polypeptide is prominent in fetal/embryonic brains, being very weak to absent in adult brain. Whilst the polypeptide sequence disclosed by Yokoyama et al. possesses about 95% "regional" sequence similarity (homology), it is nevertheless less than

half the length of the novel splice variant sequence of the present invention (461 residues shorter). These two sequences therefore only have about 44% "total" sequence homology (query match)(see page 14, line 27). More importantly, the Yokoyama polypeptide is incapable of functioning as a potassium channel. The Yokoyama polypeptide is missing the C-terminal tail of the polypeptide of the present invention and the Applicants have found that the Yokoyama polypeptide is not capable of functioning as a potassium channel (see page 17, lines 25-32). Indeed, rather than being transported into the plasma membrane, the C-terminally truncated Yokoyama polypeptide is sequestered in the endoplasmic reticulum. The claims have been amended to cover variants which have at least 85% total sequence similarity and to cover biologically active fragments thereof. Whilst it might be argued that Yokoyama is a fragment of SEQ ID No:3 (a C-terminally truncated fragment) it lacks the biological activity of a potassium channel and therefore falls outside the claim.

In view of the claim amendments reciting that the variants have to have at least 85% total sequence similarity with the sequence disclosed in SEQ ID NO:3, or be a biologically active fragment thereof, Applicants submit that the Yokoyama *et al.* reference does not anticipate the claimed invention.

THE REJECTION OF CLAIMS UNDER 35 USC § 103(a)

Claim 9 stands rejected as being obvious over Yokoyama *et al.* in view of Li *et al.* (WO 96/03415). In view of the fact the protein of Yokoyama et al. is not biologically active, in the sense of being a potassium channel, and shares only about 44% total sequence similarity with the protein of the present invention, and in view of the claim amendments which takes Yokoyama et al. outside of the claim scope, the Applicants submit that the claimed invention cannot be considered obvious over Yokoyama et al. in combination with Li *et al.*